Docket No.: 511582001621
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Daniel E. AFAR et al.

Application No.: 10/010,667

Filed: December 6, 2001

For: PEPTIDES DERIVED FROM STEAP 1
 (as amended)

Art Unit: 1642

Examiner: Gary B. Nickol, Ph.D.

DECLARATION OF JEAN M. GUDAS, PH.D.
UNDER 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

 I, Jean M. Gudas, declare as follows:

 1. I am currently Director of Antibody Development at Agensys, Inc., in Santa Monica, California. I am responsible for supervising the generation of antibodies to proteins contemplated as targets for antibody-based diagnosis and therapy in tumors. I have extensive experience in scientific matters related to oncology and have been practicing in this field for almost 20 years, since I received my Ph. D. in Public Health/Environmental Health Sciences from UCLA in 1985. A copy of my *curriculum vitae* is attached as Exhibit A.

sd-195979

2.   The above-referenced application concerns, among other things, a protein designated STEAP-1 that is produced in various cancers. The protein and certain of its fragments are able to raise antibodies that are immunoreactive with this protein. We have found that in prostate cancer, administration of monoclonal antibodies immunoreactive with STEAP-1 both inhibit the growth of the tumor and lower the levels of PSA secreted into the bloodstream.

3.   Specifically, we conducted an experiment wherein mice were injected with 2×10^6 LAPC9 prostate tumor cells subcutaneously. Six groups of 10 mice each were used. In all cases, the mice were injected with the LAPC9 cells and then treated according to various protocols. In each group, the mice were injected with test solutions two times per week for a total of 12 injections wherein the last day of injection was day 40. The first injection was on the same day as the injection of tumor cells. Injection was by the intraperitoneal route. Group I received PBS injections, Group II received control anti-KLH antibody injections, Group III received the anti-STEAP-1 antibody 120.545 at 500 μg per dose; Group IV received 120.545 antibody at 100 μg per dose; Group V received anti-STEAP-1 antibody 92.30 at 500 μg per dose and Group VI received 92.30 antibody at 100 μg per dose. Tumor volume was monitored over the treatment period.

4.   Exhibit B shows the results. As indicated, tumor growth in the controls (Groups I and II) and at dosages of 100 μg of the two antibodies tested was consistently higher than tumor growth exhibited when either antibody was administered at 500 μg per dose. These results are shown in a different form in Exhibit C which shows, on the left, median tumor volume on day 40. It is clear that administration of either STEAP-1 antibody is effective in decreasing tumor volume.

5.   Similarly, the right hand graph of Exhibit C demonstrates that both anti-STEAP-1 antibodies reduce the levels of PSA in the mouse.

6.   I conclude from these results that antibodies raised against STEAP-1 are effective in inhibiting the growth of prostate tumors.

I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Executed at Santa Monica, California, on 29th April 2004.

(Jean M. Gudas)

EXHIBIT A.

CURRICULUM VITAE

Jean M. Gudas, Ph.D.

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Pacific Palisades, CA 90272
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AREAS OF EXPERTISE

Antibody directed cancer therapies
Signal transduction pathways
Tumor-host cell interactions

EDUCATION:

1975	B.S.	*Magna cum laude*, Microbiology, University of Rhode Island, Kingston, R.I.
1977	M.S.	Microbiology, Oklahoma University Health Sciences Center, Oklahoma City, OK
1982	MPH	Public Health, Environmental Health Sciences, University of California, Los Angeles, CA
1985	Ph. D	Public Health, Environmental Health Sciences, University of California, Los Angeles, CA

POSTDOCTORAL TRAINING:

1985 to 1991   Postdoctoral Research Fellow, Division of Cell Growth and Regulation, Dana Farber Cancer Institute, Boston, MA.

PROFESSIONAL EXPERIENCE:

1977 to 1978   Research Assistant, Department of Hematology, City of Hope National Medical Center, Duarte, CA
Early gene therapy efforts on Gaucher's disease

1978 to 1979   Staff Research Associate, Department of Gastroenterology, Wadsworth VA Hospital, Los Angeles, CA
Regulation of type II drug metabolizing enzymes

1979 to 1980   Research Associate, Genex Corp., Gaithersburg, MD

Regulatory pathways/enzymes for detoxification of environmental pollutants

1991 to 1996   Senior Staff Fellow, National Cancer Institute, Division of Cancer Treatment, Bethesda, MD

- Examined role(s) and signaling pathways controlled by proto-oncogenes c-myb, MDM2 and tumor suppressor genes BRCA1, p53, and p21$^{CIP1/Waf1}$ in breast cancer genesis and progression
- Studied contribution of oncogenes and loss of tumor suppressor genes to chemotherapeutic drug resistance
- Directed and supervised research activities of M.D. Oncology Fellows, visiting scientists, research technicians, graduate and summer students
- Organized inter-departmental group seminars and outside speakers
- Subcommittee to design and implement breast cancer prevention strategy and program at NCI

1996 to 2001   Research Scientist I- III, Amgen Inc., Cancer Biology Dept. Thousand Oaks, CA

- Directed research efforts using DNA microarrays and other technologies to identify and validate molecular targets in cancer- discovered novel cyclin E2
- Directed project to study the role of Vitamin D receptor in regulating breast and prostate cancer cell differentiation
- Led screening efforts to identify inhibitors of nuclear receptors
- Identified and studied role of Aldo Keto Reductase genes in drug resistance
- Initiated efforts to map and distinguish signal transduction pathways controlled by the EGF, Her2/neu and c-met receptors
- Directed and coordinated all efforts including screening, biochemical and cell-based assays and animal models to identify and validate antibodies that blocked the function of a tyrosine kinase growth factor pathway – a human inhibitory antibody to this target will likely to enter clinical trials in early 2003
- Represented Cancer Biology department on company-wide oncology strategy task force, leukemia working group and product licensing teams.
- Conceived and implemented strategy to developed CHO cell line with improved yields of mammalian proteins- All mammalian proteins at Amgen are now produced using this strain.
- Lead scientist on Amgen due diligence scientific evaluation teams that resulted in licensing of CD22 with Immunomedics and acquisition of Kinetix

2001- 2003:   Scientist II-Senior Scientist, Abgenix Inc., Fremont, CA

- Lead scientist on four internal and one collaborative oncology antibody project in areas relating to tumor hypoxia, angiogenesis, growth control and tumor specific cell surface membrane proteins.
- Lead scientist in evaluating and implementing company platform for antibody drug conjugates- Coordinated strategies and assays for selecting and optimizing antibody mediated drug delivery *in vitro* and *in vivo*
- Coordinated research efforts with outside collaborator that led to 2001 IND and patent filing for Muc18 antibodies to treat metastatic melanoma
- Designed and managed animal studies with outside contractor(s) to support IND filings for two antibody therapeutics
- Wrote Pharmacology section of IND for ABX-MA1 IND filing
- Coordinated research efforts with outside collaborator that led to IND and patent filing for ABX-IL8 in the oncology setting
- Coordinated and managed patent filings for four proprietary antibodies for treating human cancers
- Proposed, reviewed and chaperoned 7 new cancer antibody targets through Antigen Sourcing Team and Oncology Therapeutic Area Team review processes
- Member of Lexicon, Curagen, Immunotoxin and Intracellular drug delivery subteams
- Coordinated scientific efforts of Oncology Therapeutic Area Team
- Coordinated oncology collaborations with academic groups

2003- Present: Director, Antibody Development, Agensys Inc., Santa Monica, CA

- Direct all internal efforts to generate murine and human hybridomas and evaluate their functions in vitro and in vivo

AREAS OF TECHNICAL EXPERTISE:

Cell Biology

Established cell based screening platform for high throughput assay of nuclear receptors

Culture of primary, normal, immortalized and tumorigenic human breast and prostate epithelial cells

DNA transfections

Cell fusions and hybridoma generation

Cell synchronization

FACS analyses

Immunocytochemistry

Bioassays for proliferation, transformation and differentiation

Retrovirus construction and infection of cells

Primary and secondary cytotoxicity assays
Cell-based migration and invasion assays for tumor and endothelial cells
In vivo xenograft tumor models for multiple cancer targets
Antibody generation and screening

Molecular Biology
DNA microarrays and clustering analysis
RNA analyses including nuclear run-on transcription assays, Northern blots, primer extension, RNAse protection assays and reverse transcription PCR analyses
Gene cloning
DNA analyses including Southern blot hybridizations and PCR amplification
Routine procedures including DNA sequencing, restriction enzyme digestion, gel electrophoresis, subcloning and construction of expression vectors

Protein Analyses
Western, immunoblot and immunoprecipitations
Baculovirus protein expression systems

TEACHING EXPERIENCE:

1975 to 1977	Teaching Assistant in Microbiology, University of Oklahoma Health Sciences Center
1981 to 1983	Teaching Assistant and Lecturer, University of California, Los Angeles School of Public Health
1991 to 1995	Mentoring of medical fellows, graduate and summer students in their laboratory research projects at NCI

AWARDS and HONORS:

1971 to 1974	Rhode Island State Scholarship recipient Dean's list, all semesters
1974 to 1975	Honors Program, University of Rhode Island
1975	Mortar Board National Honor Society
1975 to 1977	Graduate Assistantship Program, Oklahoma University Health Sciences Center
1975 to 1977	Graduate Assistantship Program, Oklahoma University Health Sciences Center
1980 to 1982	U.S. Public Health Traineeship, UCLA School of Public Health

1983 to 1985	Individual Predoctoral Fellowship Award, Associated Western Universities
1987 to 1991	Individual National Research Service Award-NCI

PROFESSIONAL SOCIETIES:

Women in Cancer Research
American Association for the Advancement of Science
American Society of Microbiology
American Association for Cancer Research

PROFESSIONAL ACTIVITIES:
>DOD National Breast Cancer Integration Panel Member-1999
>Chairperson- Basic Biology Session, Basic and Clinical Aspects of Breast
>Cancer, 1997 Keystone Meeting
>Reviewer- DOD Army Breast Cancer Program 1996- 2000
>Co-organizer Washington, D.C. Regional Cell Cycle Interest Group
>Co-organizer NCI Breast Biology Interest Group
>Co-organizer of NCI Medicine Branch Seminar series
>Ad hoc reviewer for Int. J. Cancer Res., Cancer Res., Mol.
>Carcinogenesis, Cancer Letters and Biochem. Biophys. Acta and Oncogene

PUBLICATIONS:

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Glaumann, H., **J. M. Gudas,** N. Kaplowitz and C. Von Bahr. Inhibition of hepatic metabolism of azathioprine by furosemide in human liver *in vitro*. Biochem. Pharmacol. **29**: 1439, 1980.

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Mian, B.M., Dinney, C.P., Bermejo, C.E., Sweeney, P., Tellez, C., Yang, X-D., **Gudas, J.M.**, McConkey, D.J. and Bar-Eli, M. Fully human Anti-IL8 antibody inhibits tumor growth in orthotopic bladder cancer xenografts via downregulation of matrix metalloproteases and NF-kB. (Manuscript submitted to Clin. Cancer Res.)

PATENTS and APPLICATIONS

Feige, U., Liu, Chuan-Fa, Cheetham, J.C., Boone, T.C. and **J.M. Gudas.** US Patent application 09-563,286 Modified peptides as therapeutic agents, May 3, 2000.
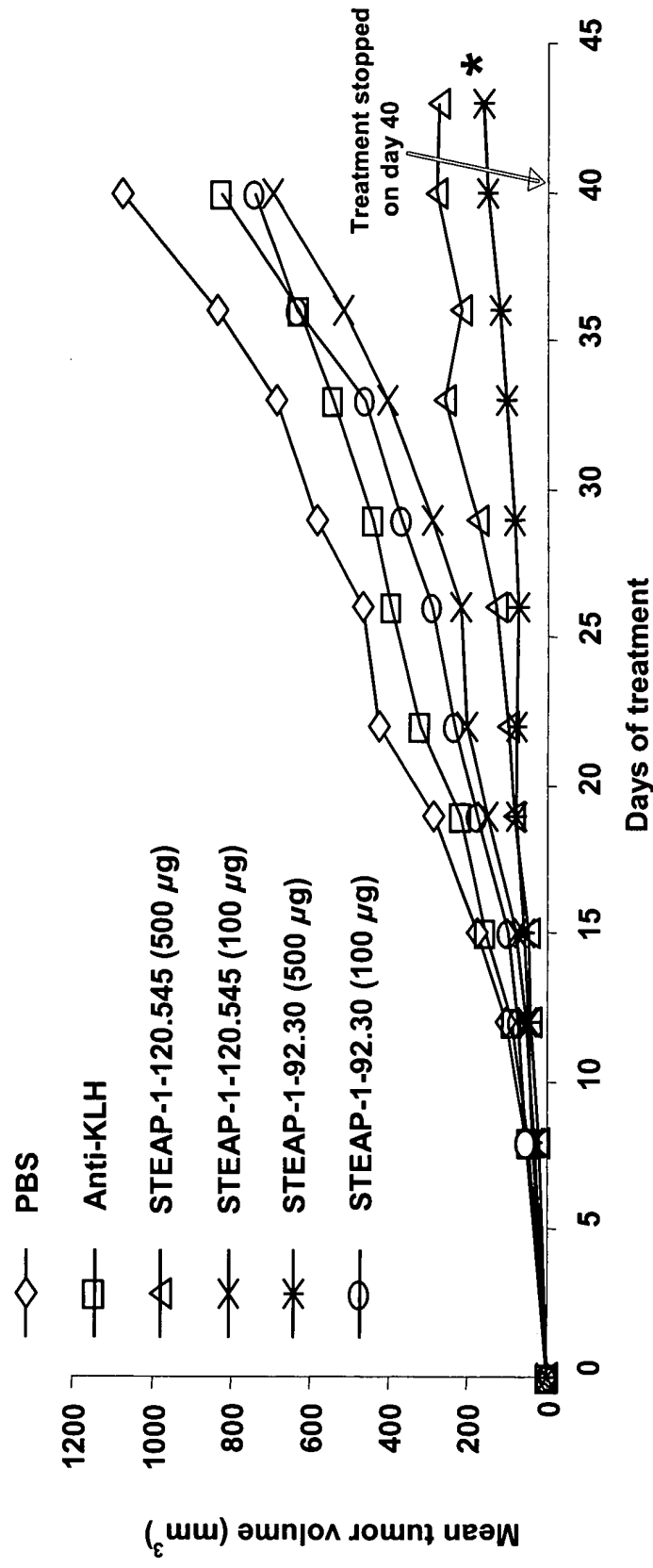
Hu, S. and **Gudas, J.M**. Overexpressing cyclin D in an eukaryotic cell line. US Patent 6,210,924 B1 April 3, 2001.

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Exhibit B: Effect of STEAP-1 MAbs on the Growth of LAPC9 Human Prostate Cancer Xenograft in Mice

Legend:
- PBS
- Anti-KLH
- STEAP-1-120.545 (500 μg)
- STEAP-1-120.545 (100 μg)
- STEAP-1-92.30 (500 μg)
- STEAP-1-92.30 (100 μg)

X-axis: Days of treatment

Y-axis: Mean tumor volume (mm³)

Treatment stopped on day 40

◆ Treatment started on the same day of subcutaneous tumor cell injection (2×10^6/mouse; n=10/group)

◆ MAb ip injection – 100 or 500 μg/dose, 2/week, 12 injections (last day – d40)

* Significant difference compared to PBS and anti-KLH controls with $p<0.05$

Exhibit C: Effect of STEAP-1 MAbs on the Growth of LAPC9 Human Prostate Cancer Xenografts in Mice

Median tumor volume (mm³) on day 40

Mean PSA levels on day 40